



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>4</sup> : A61K 31/07		A1	(11) International Publication Number: WO 86/ 06275 (43) International Publication Date: 6 November 1986 (06.11.86)
(21) International Application Number: PCT/US86/00780 (22) International Filing Date: 17 April 1986 (17.04.86) (31) Priority Application Numbers: 725,480 845,256 (32) Priority Dates: 22 April 1985 (22.04.85) 28 March 1986 (28.03.86) (33) Priority Country: US (60) Parent Application or Grant (63) Related by Continuation US 725,480 (CIP) Filed on 22 April 1985 (22.04.85) (71) Applicant (for all designated States except US): AVON PRODUCTS, INC. [US/US]; 9 West 57th Street, New York, NY 10019 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : WILMOTT, James, M. [US/US]; 137 Rolling Ridge Road, West Milford, NJ 07480 (US). ZNAIDEN, Alexander, P. [US/US]; 155 Johnstown Road, Sloatsburgh, NY 10947 (US). (74) Agent: BENDER, Michael, S.; Suite 127, Harmon Cove Towers, Secaucus, NJ 07094 (US). (81) Designated States: AU, DE (European patent), FR (Eu- ropean patent), GB (European patent), IT (European patent), JP, US. Published With international search report.	
(54) Title: COMPOSITION AND METHOD FOR REDUCING WRINKLES			
(57) Abstract			
<p>Stable retinol compositions. The compositions comprise retinol, a volatile silicone and a mutual solvent for the retinol and silicone. Preferred compositions contain retinol, cyclomethicone and ethanol. Where the retinol level in the compositions is between 0.005 and 1.0 weight percent, the compositions may be topically applied to the skin in areas where fine lines, wrinkles or other signs of aging exist. Such topical application results in a reduction in wrinkles and fine lines and improves skin quality. Where the compositions contain more than 0.005 to 1.0 weight percent retinol they may be diluted with cosmetically acceptable carriers or vehicles, preferably water in oil emulsions to reduce the retinol level and topically applied.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
BB	Barbados	HU	Hungary	NL	Netherlands
BE	Belgium	IT	Italy	NO	Norway
BG	Bulgaria	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali		
FR	France				

## COMPOSITION AND METHOD FOR REDUCING WRINKLES

This application is a continuation-in-part of prior copending United States Application Serial No. 845,256, filed March 28, 1986, which, in turn, is a continuation-in-part of prior copending United States application Serial No. 725,480 filed April 22, 1985, which, in turn, is a continuation-in-part of prior United States application Serial No. 702,328, filed February 15, 1985, now abandoned.

Background of the Invention

## a) Field of the Invention

This invention relates to stable compositions containing retinol which upon topical application to the skin cause wrinkle effacement and other beneficial effects. It also relates to use of such compositions in combination with or including moisturizers.

## b) State of the Art

Retinol (Vitamin A), though believed to cause beneficial skin effects, has never been successfully formulated in a composition suitable for topical application. It has now been discovered that retinol can be formulated in stable form and can be administered topically in a cosmetic base with minimal irritant side effects. Further, when topically applied as taught by the invention, retinol causes effacement of facial fine lines and wrinkles, increases skin elasticity, reduces pore size and improves skin texture.

Summary of the Invention

This invention relates to stable cosmetic compositions for reducing facial lines and wrinkles and otherwise enhancing

skin quality and to methods of using that composition. The compositions comprise retinol coupled with a volatile silicone carrier by means of a mutual solvent. The preferred compositions, which result in optimum stability and efficacy, are those containing volatile silicones, such as cyclomethicone, ethanol as the mutual solvent and retinol. When applied to the skin, the compositions contain 0.005 to 1.0 weight percent retinol. Most preferred compositions for application to the skin contain 0.01 to 0.50 weight percent retinol. The stable compositions of the invention may be formulated with more concentrated levels of retinol and may be diluted to suitable levels of retinol for application to the skin by means of cosmetically acceptable carriers. The compositions may additionally contain or may be applied in conjunction with a moisturizer to enhance the beneficial effects and sensory comfort of the composition.

#### Detailed Description of the Invention

It has been discovered that a cosmetic composition containing retinol in a volatile silicone vehicle is stable, and upon topical application reduces fine lines and wrinkles and otherwise beneficially affects skin quality. More particularly, it has been discovered that a stable retinol composition can be formulated using a volatile silicone carrier and a mutual solvent for the silicone and retinol. Compositions containing 0.005 to 1.0 weight percent retinol can reduce facial fine lines and wrinkles with minimal irritant effects.

The stable retinol compositions of the invention are formulated in a vehicle containing a volatile silicone.

With such a vehicle, retinol levels needed to achieve beneficial effects are minimized and the potential for irritant effects to the skin by retinol are greatly diminished. Moreover, retinol is stable when formulated in the silicone  
5 containing compositions of the invention, in contrast to other conventional cosmetic carriers.

The compositions of the invention may be formulated as alcohol lotions containing 0.005 to 1.0 weight percent retinol, in which case they may be applied directly to the skin, or as  
10 more concentrated alcohol lotions containing higher levels of retinol, in which case prior to application they are diluted by means of a cosmetically acceptable carrier to a 0.005 to 1.0 weight percent retinol level. In the formulations of the invention, water is optimally minimized or eliminated to  
15 maximize the stability of retinol and to minimize the potential for separation of the oil and water. No more than 2 percent water should be present.

When the compositions of the invention are formulated for application as alcohol lotions, a preferred mutual solvent  
20 for the volatile silicone and the retinol is ethanol. Preferred silicones are volatile low viscosity polysiloxanes, such as cyclomethicones, including cyclomethicone tetramer and pentamer. In the alcohol lotion formulation, the retinol level is most preferably 0.10 to 0.50 weight percent. The weight ratio of  
25 silicone to mutual solvent is optimally about 6:4.5 when cyclomethicone tetramer is the silicone and ethanol is the mutual solvent. At that level, stability, comfort and aesthetics are optimized. For stability the silicone should be

at least 20 weight percent of the alcohol lotion composition. The ethanol or other mutual solvent, such as isopropyl alcohol, should be present in an amount sufficient to couple the silicone and retinol and yet not exceed the level at which tearing, stinging or other discomfort is observed. Generally, levels of ethanol between 25 to 60 weight percent will be acceptable.

An alcohol lotion composition may additionally contain emollients, and thickening agents for aesthetic effects such as lubrication and tactile perception. The emollients which may be present include all standard emollients which are miscible in the alcohol lotion. Preferred emollients include ethyl hexyl palmitate, neopentyl glycol dicaprate and ethylene glycol dicaprate. The quantity thereof is dependent upon tactile perception and compatibility with the silicone and solvent. Levels up to 15 weight percent will commonly be acceptable.

Ultraviolet absorbers or sunscreens, antioxidants and the like may also be present in the compositions of the invention to enhance the stability of retinol against degradation. Examples of ultraviolet absorbers which may be employed in the alcohol lotion formulation include octyl dimethyl PABA and benzophenone-3. Examples of suitable antioxidants and preservatives include butylated hydroxytoluene, BHA, imidazoline urea and methylparaben. Thickeners are those which are compatible with the overall composition, such as bentones, fumed silica and ethyl cellulose. Dyes, fragrance and other cosmetic additives may also be present, if desired, provided they do not react with any component of the composition and do not interfere with the homogeneity of the composition. The stable retinol/

silicone compositions of the invention may be formulated in concentrated form, that is, may be formulated with higher levels of retinol, without loss of stability. However, when so formulated the compositions of the invention are diluted to produce  
5 retinol levels of 0.005 to 1.0 weight percent, preferably 0.01 to 0.50 weight percent, prior to application to the skin. In preferred practice, dilution may be effected by means of a water in oil emulsion. In such an emulsion, silicones of the type employed in the alcohol lotion are preferred. The silicone  
10 will commonly be 15 to 35 weight percent of the composition which is applied to the skin and most preferably about 20 weight percent of the composition.

A suitable emulsion for dilution of the compositions of the invention may be formed by first mixing the volatile  
15 silicones with silicone dimethicone copolyol. The remaining components of the emulsion, such as emulsifiers, emulsion stabilizers, preservatives and sunscreens, are dissolved or dispersed in water. The aqueous phase is then very slowly added to the cyclomethicone phase with vigorous homogenization  
20 which is continued until an acceptable viscosity is achieved.

The aqueous phase of the emulsion should contain preservatives of the type indicated for the alcohol lotion. It is also desirable that emulsion stabilizers, such as sodium  
chloride be employed.

25 The relative ratios of the water and oil phases is optimally 2 to 1. Deviations from this ratio result in changes in the viscosity of the system. The limits of permissible variation are dependent upon cosmetically acceptable viscosities.

When the composition of the invention is formulated in concentrated form for application in an emulsion of the type described, the emulsion and composition are blended prior to application. The quantity of emulsion employed is dependent on the concentration of the retinol composition of the invention. For example, if the retinol composition contains 4 weight percent retinol, sufficient emulsion must be added to reduce the percent weight of retinol to the 0.005 to 1.0 range, or more preferably to the 0.01 to 0.50 range.

The compositions of the invention, when formulated in concentrated form, can also be diluted to the appropriate retinol level for application by means of other cosmetically acceptable carriers or vehicles which are miscible with the retinol composition of the invention. Other cosmetic additives may be employed, either in the compositions of the invention or in those compositions when diluted with a suitable vehicle, provided they do not react with the retinol and are otherwise compatible with the compositions.

The compositions formulated as described above are topically applied to the skin on concentration which result in application of 0.005 to 1.0 weight percent retinol, preferably 0.01 to 0.50 weight percent. They are applied in the areas where fine lines, wrinkles, dry or inelastic skin or large pores are observed. Optimally a moisturizer is applied with or after application of the retinol compositions to enhance the tactile comfort associated with application of the compositions and to enhance the wrinkle effacement and other benefits achieved by the compositions.



Alternatively, it has been discovered that moisturizing efficacy can be achieved in the compositions of the present invention containing the retinol, thereby precluding the need for a separate moisturizer. Therefore, preferred compositions of the invention can be formulated to include moisturizing components that are compatible with the alcohol lotion or silicone emulsion to a level of up to 35% by weight of the final formulation. Preferred moisturizing ingredients suitable for use the preferred compositions of the invention may be selected from the group comprising gly acrylic polymer (Lubragel), petrolatum, ethylhexyl palmitate, and hyaluronic acid sodium salt.

With daily application, skin texture, color and tone will improve. Wrinkles and fine lines will be reduced with minimal irritant effects.

The following examples are illustrative of the invention and of the beneficial effects which can be achieved with the compositions of the invention and should not be construed as limiting.

Example 1

A preferred alcohol lotion composition in accordance with the invention was formulated as follows (all quantities are stated as weight percents):

A retinoid blend was formulated containing:

48.01264	Polysorbate 20
48.01264	Retinol
3.00000	BHT
.75000	BHA
.09977	Retinol Acetate
.09977	Retinol Palmitate
.02494	Carotene
.00024	Apocarotenal

- 8 -

The blend was combined with an alcohol lotion composition to form the following composition of the invention:

#### Formulation A

	46.27776%	Cyclomethicone-Tetramer
5	35.00000%	Alcohol SD 40B Anhydrous
	5.00000%	Ethylhexyl Palmitate
	5.00000%	Octyl Dimethyl PABA
	2.00000%	Benzophenone-3
	2.00000%	Demineralized Water
10	2.00000%	Neopentyl Glycol Dicaprate
	1.50000%	Ethyl Cellulose K5000
	0.22000%	Butylated Hydroxytoluene
	1.00224%	Retinoid Blend
Total	100.00000%	

#### Example 2

A preferred emulsion was formulated as follows. A concentrated retinoid composition in accordance with the invention was formulated as follows:

	Retinoid Blend (Example 1)	4.17600
20	BHT	.16660
	Alcohol SD40B Anhydrous	33.33330
	Cyclomethicone-Tetramer	62.32410

A water in oil emulsion was formulated as follows:

	Cyclomethicone Tetramer	11.36360
25	Cyclomethicone Pentamer	5.68180
	Cyclomethicone/Dimethicone Copolyol	11.36360
	Demineralized Water	64.91370
	Sodium Chloride	1.13640
	Methylparaben	.45450
30	Stearyl ETO (20M) Alcohol	1.13640
	Triethanolamine 99%	1.25000
	Phenyl Benzimidazole	2.27270
	BHT	.22730
	Germall (Sutton Laboratories)	.20000

Before application, the concentrated retinoid composition and the emulsion are blended to form the following composition suitable for application to the skin.

#### Formulation B

	57.12406%	Demineralized Water
40	16.97770%	Cyclomethicone-Tetramer

**SUBSTITUTE SHEET**

	10.00000%	Cyclometh/dimeth Copolyol 90/10
	5.00000%	Cyclomethicone-Pentamer
	4.00000%	Alcohol SD 40B Anhydrous
	2.00000%	Phenyl Benzimidazole-5-Sulf Acid
5	1.10000%	Triethanolamine 99%
	1.00000%	Stearyl ETO (20M) Alcohol
	1.00000%	Sodium Chloride
	0.40000%	Methylparaben
	0.22000%	Butylated Hydroxytoluene
10	1.00224%	Retinoid Blend
	0.17600%	Germall
Total	100.00000%	

Example 3

A commercially available Vitamin A Alcohol Blend

- 15 (Retinol Blend) was obtained comprising the following ingredients by percent weight:

	Polysorbate 20	48.125
	Retinol	48.125
	BHT	3.000
20	BHA	0.750
		100.000%

This produced a composition which contained approximately 1.5

million units of Vitamin A activity per gram. This Retinol

Blend or composition was used to prepare the following test

- 25 formulations:

	Alcohol Lotion	Emulsion
	35.00000	4.00000
	Alcohol SD 40B Anhydrous	
	Benzophenone-3	2.00000
30	Neopentyl Glycol Dicaprate	2.00000
	Demineralized Water	2.00000
	Ethylcellulose K5000	1.50000
	Cyclomethicone-Tetramer	45.50000
	Ethyhexyl Palmitate	5.00000
35	Octyl Dimethyl PABA	5.00000
	Vitamin A Alcohol Blend	1.00000
	Fumed Silica	1.00000
	Cyclomethicone Pentamer	5.00000
	Cyclomethicone Dimethicone	
40	Copolyol	10.00000
	Sodium Chloride	1.00000
	Methylparaben	.40000
	Stearyl ETO (20M) Alcohol	1.00000
	Triethanolamine 99%	1.10000
45	Phenyl Benzimidazole	2.00000

A split face test was conducted by using the foregoing following formulations as follows. Twelve females aged 20 to 59 applied one of the test formulations to one side of their faces and the other to the other side once daily for eight weeks. Rich Moisture Cream (Avon), a moisturizer, was applied over both retinol treated areas after application of the test formulation. Thin shavings of the skin on each side of the face were taken before the test began and after the eight week test period. It was observed that the skin shavings after the test were in better condition than those before the test in nine of the twelve women. The skin of those nine women was both thicker and more organized after the test than before. There were no observable differences between the effects of the two test formulations.

15 Example 4

Rhino mouse skin studies were conducted to determine the effectiveness of retinol in normalizing epidermal skin structures. Rhino mice normally have wrinkled, sagging skin. The rhino mouse test is used as a model for showing the effects of compositions on the epidermis. In the test each set of seven mice was treated for five days/week for six consecutive weeks. Eight sets of mice were treated. The treating agents were similar to the vehicles of Formulations A and B in Examples 1 and 2 without the retinol blend and each of those vehicles with the retinol blend, with the retinol content at concentrations of 0.10, 0.25 and 0.50 weight percent. Specifically, the four silicone emulsions contained:

- 11 -

	I	II	III	IV
	Cyclomethicone-Pentamer	5.00000	5.00000	5.00000
	Cyclomethicone-Tetramer	17.50000	16.97300	16.97300
	Cyclometh/Dimeth			
5	Copolyol 90	10.00000	10.00000	10.00000
	Deminerlized Water	59.50000	59.50000	59.50000
	Sodium Chloride	1.00000	1.00000	1.00000
	Methylparaben	.40000	.40000	.40000
	Stearyl ETO (20M) Alcohol	1.00000	1.00000	1.00000
10	Triethanolamine 99%	1.10000	1.10000	1.10000
	Phenyl Benzimidazole-5-Sulf.	2.00000	2.00000	2.00000
	Alcohol SD 40B Anhydrous	2.50000	2.80000	2.50000
	Vitamin A Alcohol Blend	-----	.20000	.50000
15	Carotenoid Solution	-----	.02500	.02500
	Vitamin A Palmitate	-----	.00100	.00100
	Vitamin A Acetate	-----	.00100	.00100

The four alcohol lotion formulations contained:

	V	VI	VII	VIII
20	Alcohol SD 40B Anhydrous	35.00000	35.30000	35.00000
	Ethylhexyl Palmitate	5.00000	5.00000	5.00000
	Benzophenone-3	2.00000	2.00000	2.00000
	Octyl Dimethyl PABA	5.00000	5.00000	5.00000
	Neopentyl Glycol Dicaprate	2.00000	2.00000	2.00000
25	Deminerlized Water	2.00000	2.00000	2.00000
	Ethyl Cellulose K5000	1.50000	1.50000	1.50000
	Butylated Hydroxytoluene	.20000	.22000	.22000
	Cyclomethicone-Tetramer	46.30000	45.75300	45.75300
	Silica-Fumed	1.00000	1.00000	1.00000
30	Carotenoid Solution	-----	.02500	.02500
	Vitamin A Acetate	-----	.00100	.00100
	Vitamin A Palmitate	-----	.00100	.00100
	Vitamin A Alcohol Blend	-----	.20000	.50000

Visual observation of the skin condition during the

35 period of treatment showed a diminution of the characteristic epidermal glandular structures in the sets of mice treated with formulations containing retinol. No such change in wrinkling and sagging was observed in the mice treated with the vehicle alone.

#### 40 Example 5

A test of the effectiveness of retinol formulations of the invention in reducing damage to skin resulting from exposure

- 12 -

to sunlight, and more particularly ultraviolet wavelengths thereof, was conducted. The test was conducted using hairless mice. Sixty mice were exposed three days a week for ten weeks to 20 minutes of ultraviolet light. Thereafter the mice were divided into four groups of 5 mice each. Each group was treated with one of the four following compositions:

Emulsion

	Cyclomethicone Pentamer	5.00000	5.00000
	Cyclomethicone Tetramer	16.97300	17.50000
10	Cyclometh/Dimeth Copolyol	10.00000	10.00000
	Demineralized Water	59.50000	59.50000
	Sodium Chloride	1.00000	1.00000
	Methylparaben	.40000	.40000
	Stearyl ETO (20M) Alcohol	1.00000	1.00000
15	Triethanolamine 99%	1.10000	1.10000
	Phenyl Benzimidazole	2.00000	2.00000
	Alcohol SD 40B Anhydrous	2.00000	2.50000
	Vitamin A Alcohol Blend	1.00000	
	Carotinoid Solution	.02500	
20	Vitamin A Palmitate	.00100	
	Vitamin A Acetate	.00100	

Alcohol Lotion

	Alcohol SD 40B Anhydrous	34.50000	35.00000
	Ethylhexyl Palmitate	5.00000	5.00000
25	Benzophenone-3	2.00000	2.00000
	Octyl Dimethyl PABA	5.00000	5.00000
	Neopentyl Glycol Dicaprate	2.00000	2.00000
	Demineralized Water	2.00000	2.00000
	Ethyl Cellulose K5000	1.50000	1.50000
30	BHT	.22000	.20000
	Cyclomethicone Tetramer	45.75300	46.30000
	Fumed Silica	1.00000	1.00000
	Carotinoid Solution	.02500	
	Vitamin A Acetate	.00100	
35	Vitamin A Palmitate	.00100	
	Vitamin A Alcohol Blend	1.00000	

Treatment was effected daily for five weeks. Another four groups of seven mice each were similarly treated for ten weeks.

After treatment, the skin repair of the UV-induced damage was observed. The skin of mice treated with retinol-

- 13 -

containing formulations had up to a twofold greater repair zone than the skin of mice treated with either vehicle. This greater repair can be correlated with visual improvement in the skin. That is, under similar treatment with retinol, the human skin

5 can be expected to show a diminution in lines and wrinkles.

#### Example 6

A six month study was conducted to determine the ability of retinol to produce visible effacement of facial crowsfeet, lines and wrinkles and textural skin improvements.

10 The test was done on a split face basis with half of the test population applying Formulation C and the other half using Formulation D:

	C	D
15	Cyclomethicone-Tetramer 15.00000	45.30000
	Cyclomethicone-Pentamer 5.00000	-----
	Cyclomethy/Dimeth Copolyol 90/10 10.00000	-----
	Demineralized Water 59.50000	2.00000
	Sodium Chloride 1.00000	-----
	Methylparaben .40000	-----
20	Stearyl ETO (20M) Alcohol 1.00000	-----
	Triethanolamine 99% 1.10000	-----
	Phenyl Benzimidazole-5-Sulf Acid 2.00000	-----
	Alcohol SD 40B Anhydrous 4.00000	35.00000
	Vitamin A Alcohol Blend 1.00000	1.00000
25	Butylated Hydroxytoluene -----	.20000
	Ethylhexyl Palmitate -----	5.00000
	Benzophenone-3 -----	2.00000
	Octyl Dimethyl PABA -----	5.00000
	Neopentyl Glycol Dicaprate -----	2.00000
30	Ethyl Cellulose K5000 -----	1.50000
	Silica-Fumed -----	1.00000

Crowsfeet, suborbital areas, cheeks and lips were treated.

Application was done once a day.

Within two months of commencement of the test, the

35 benefits of the retinol formulations were evident. Textural skin improvement was observed in the crowsfeet and cheek areas

- 14 -

of the panelists. A softening or smoothing in fine lines in the crowsfeet and suborbital areas was also noted.

At the end of three months, line reduction in the crowsfeet and suborbital area appeared in more panelists than at the end of two month period. There was also a greater improvement in skin texture in the crowsfeet and cheek areas between the 2 and 3-month observations. Further, textural improvement in the suborbit of the eye and decreased dryness in the crowsfeet, suborbital and cheek areas were apparent.

After four months of treatment, the skin areas treated with the formulations of the invention showed marked improvement. Skin dryness and texture had improved in all four treated areas. Lines and wrinkles had diminished in the crowsfeet suborbital and cheek areas. The skin in the crowsfeet and suborbital areas also showed a significant improvement in firmness.

By the end of six months of treatment, the benefits of the formulations of the invention were fully apparent. With the exception of the lip area, there was a visual improvement in the treated skin's texture and the treated skin was significantly smoother to the touch. There had also been a significant reduction in the number of fine lines and/or wrinkles in the crowsfeet and suborbital regions and to a lesser extent on the cheeks.

#### Example 7

A water in oil emulsion in accordance with the invention was formulated as follows:



- 15 -

		g/ g
	Volatile Silicone Tetramer	15.0
	Volatile Silicone Pentamer	5.0
	Dimethicone Copolyol	10.0
	Water	q.s.
5	Eusolex 232	2.0
	TEA 99%	1.1
	Sodium Chloride	1.0
	Ethanol	4.0
	Retinoid Blend 1.5MM units (Example 1)	1.0
10	Bridge 78 (20) ethoxylated Stearyl Ether	1.0

This product possesses excellent aesthetic properties and the retinol is acceptably stable in this vehicle over the intended usage period. Its efficacy has been established via the Rhino mouse test described in Example 4.

#### 15 Example 8

The stability of retinol in the compositions of the invention was tested. The formulations tested were as follows:

#### Formulation C

	Cyclomethicone-Tetramer	58.1481
20	Anhydrous Alcohol	33.3333
	Retinoid Blend	8.3520
	BHT	0.1666
		100.0000%

#### Formulation D

25	Cyclomethicone-Tetramer	45.500
	Anhydrous Alcohol	35.000
	Ethylhexyl Palmitate	5.000
	Octyl Dimethyl PABA	5.000
	Benzophenone-3	2.000
30	Neopentyl Dicaprate	2.000
	Demineralized Water	2.000
	ECK-5000	1.500
	Retinol Blend	1.000
	Fumed Silica	1.000
35		100.000%

- 16 -

Formulation E

	Cyclomethicone-Tetramer	39.80
	Anhydrous Alcohol	40.00
	Retinoid Blend	10.00
5	BHT	0.20
		<u>100.00</u>

Formulation F

	Cyclomethicone-Tetramer	69.53
	Anhydrous Alcohol	20.00
10	Retinol Blend	10.00
	BHT	0.20
	Carotinoid-Solution	0.25
	Retinyl Palmitate	0.01
15	Retinyl Acetate	0.01
		<u>100.00%</u>

Formulation G

	Cyclomethicone-Tetramer	34.765
	Ethylhexyl Palmitate	25.000
	Octyl Dimethyl PABA	25.000
20	Anhydrous Alcohol	10.000
	Retinol Blend	5.000
	Carotinoid Solution	0.125
	BHT	0.100
	Retinyl Palmitate	0.005
25	Retinyl Acetate	0.005
		<u>100.000%</u>

Formulation H

	Anhydrous Alcohol	56.00
	Cyclomethicone-Tetramer	22.00
30	Octyl Dimethyl PABA	8.00
	Ethylhexyl Palmitate	5.00
	Benzophenone-3	3.00
	Neopentyl Dicaprate	2.00
	Demineralized Water	2.00
35	Hydroxypropyl Cellulose	1.30
	Retinol Blend	0.50
	BHT	0.20
		<u>100.00%</u>

Formulation I

40	Anhydrous Alcohol	55.50
	Cyclomethicone-Tetramer	22.00
	Octyl Dimethyl PABA	8.00
	Ethylhexyl Palmitate	5.00
	Benzophenone-3	3.00
45	Neopentyl Dicaprate	2.00

- 17 -

	Demineralized Water	2.00
	Hydroxypropyl Cellulose	1.30
	Retinol Blend	1.00
	BHT	0.20
5		<u>100.00%</u>

The retinol blend used in the foregoing formulations was the same as the Vitamin A Alcohol Blend of Example 3, namely:

	Polysorbate 20	48.125
	Retinol	48.125
	BHT	3.000
	BHA	0.750
10		<u>100.000%</u>

The retinoid blend used in the foregoing formulations was as follows:

15	Polysorbate 20	48.01264
	Retinol	48.01264
	BHT	3.00000
	BHA	0.75000
	Retinyl Palmitate	0.09977
20	Retinyl Acetate	0.09977
	Carotene	0.02494
	Apocarotenal	0.00024
		<u>100.00000%</u>

The Carotinoid Solution was as follows:

25	Ethylhexyl Palmitate	98.988
	Beta-Carotene	1.000
	Canthaxanthine	0.002
	Apocarotenal	0.010
		<u>100.000%</u>

30 The results were as follows:

100 o F

#### Formulation

	<u>Week</u>	<u>C</u>	<u>D</u>	<u>E</u>	<u>F</u>	<u>G</u>	<u>H</u>	<u>I</u>
	0	---	---	---	---	---	---	---
35	1	---	92%	99%	94%	103%	104%	102%
	2	99%	88%	98%	97%	103%	110%	98%
	3	102%	81%	---	---	---	---	---
	4	100%	---	---	97%	104%	108%	87%

- 18 -

6	101%	80%	98%	93%	100%	---	---
8	97%	79%	---	89%	95%	94%	95%
12	---	82%	93%	89%	97%	87%	94%

Room Temperature

5

Formulation

	<u>Week</u>	<u>C</u>	<u>D</u>	<u>E</u>	<u>F</u>	<u>G</u>	<u>H</u>	<u>I</u>
	0	100%	100%	100%	100%	100%	100%	100%
	1	---	---	---	---	---	108%	100%
	2	---	101%	---	---	---	112%	101%
10	3	102%	94%	---	---	---	---	---
	4	101%	---	---	---	---	104%	99%
	6	100%	98%	---	---	---	---	---
	8	99%	96%	---	---	---	106%	104%
	12	99%	87%	98%	96%	101%	102%	99%

15

Example 9

An alternatively preferred emulsion was formulated by forming a composition in accordance with the invention as follows:

20	Retinoid Blend (Example 1)	0.1740
	BHT	0.1666
	Alcohol SD40B Anhydrous	33.3333
	Cyclomethicone-Tetramer	66.3238
	Beta-Carotene	0.0023

A water-in-oil emulsion was formulated as follows:

25	Cyclomethicone-Tetramer	7.38560
	Cyclomethicone-Pentamer	3.97800
	Cyclometh/Dimeth Copolyol 90/10	11.36360
	Petrolatum	5.68180
	Ethylhexyl Palmitate	5.68180
30	Demineralized Water	36.15350
	Sodium Chloride	1.13640
	Methylparaben	0.45450
	Stearyl ETO (20M) Alcohol	1.13640
	Gly Acrylic Polymer (Lubragel)	22.72730
35	Hyaluronic Acid Sod. Salt	0.05110
	Triethanolamine 99%	1.55000
	Phenyl Benzimidazole-5-Sulf Acid	2.27270
	Butylated Hydroxytoluene	0.22730
	Germall	0.20000

40

As in prior examples, before application, the concentrated retinol composition and the emulsion were blended

SUBSTITUTE SHEET

together to form the following composition suitable for topical application to the skin.

Formulation J

	Demineralized Water	31.81508
5	Gly Acrylic Polymer (Lubragel)	20.00020
	Cyclomethicone-Tetramer	14.45792
	Cyclometh/Dimeth Copolyol 90/10	10.00000
	Cyclomethicone-Pentamer	3.50064
	Petrolatum	5.00000
10	Ethylhexyl Palmitate	5.00000
	Alcohol SD 40B Anhydrous	4.00000
	Phenyl Benzimidazole-5-Sulf Acid	2.00000
	Triethanolamine 99%	1.36400
	Stearyl ETO (20M) Alcohol	1.00000
15	Sodium Chloride	1.00000
	Hyaluronic Acid Sod. Salt	0.04500
	Methylparaben	0.40000
	Butylated Hydroxytoluene	0.22000
	Retinoid Blend (Example I)	0.02088
20	Germall	0.17600
	Beta-Carotene	0.00028
		100.00000%

It will be noted that this composition (Formulation J) and that of Example 10 below includes moisturizing ingredients such as gly acrylic polymer (Lubragel), petrolatum, ethylhexyl palmitate, and hyaluronic acid sodium salt.

Example 10

A split face test was conducted using the following emulsion formulation:

30	Demineralized Water	32.07848
	Gly Acrylic Polymer (Lubragel)	20.00020
	Cyclomethicone-Tetramer	14.45852
	Cyclometh/Dimeth Copolyol 90/10	10.00000
	Cyclomethicone-Pentamer	3.50064
35	Petrolatum	5.00000
	Ethylhexyl Palmitate	5.00000
	Alcohol SD 40B Anhydrous	4.00000
	Phenyl Benzimidazole-5-Sulf Acid	2.00000
	Triethanolamine 99%	1.10000
40	Stearyl ETO (20M) Alcohol	1.00000
	Sodium Chloride	1.00000

	Hyaluronic Acid Sod. Salt	.04500
	Methylparaben	.40000
	Butylated Hydroxytoluene	.22000
	Retinoid Blend (Example I)	.02088
5	Germall	.17600
	Beta-Carotene	.00028

Sixteen females aged 30-54 applied the test formulation to one side of their face twice daily for six weeks, the other side remained untreated. A leading clinical dermatologist observed a significant reduction in the appearance of the signs of facial aging including: diminution of skin lines and an improvement in the look and feel (texture) of facial skin.

#### Example 11

The panelists who participated in the study in Example 10 were instrumentally assessed for improvement in facial lines via digital image processing of skin surface replicas (Image Analysis) and by Optical Profilometry, a measure of the degree of skin surface smoothness. After 6 weeks of product usage, there was a 26% reduction in skin lines as measured by Image Analysis, and there was a 41% improvement in skin smoothness as shown by Optical Profilometry.

#### Example 12

The ability of an electric current to flow through the stratum corneum provides an indirect measurement of the corneum's water content. The panelists who participated in the study in Example 10 were assessed for moisturization using an IBS impedance/conductance meter. At least twelve hours elapsed between the last product application and the skin conductance measurement. The data clearly showed that the treated side was more moist (higher conductance readings at all measurement time

points). Further, the untreated control side of the face decreased in relative moisture content while the test side increased. Thus, the objective measurement and substantiation of the stratum corneum's electrical conductivity showed a significant enhancement in facial skin moisture content.

#### Example 13

The effectiveness of Formulation J in Example 9 on Skin biomechanical properties was evaluated by the in-vivo extensometer. One forearm site of thirteen panelists and one leg site from 10 panelists were treated with the composition of Formulation J. The contralateral forearm or leg respectively served as the untreated control. Both single and multiple applications were measured for a usage period of up to seven days. The results from this study indicated a product induced change in the skin's biomechanical properties. There was a 36% improvement in skin extensibility/elasticity immediately after product application, a 26% improvement for up to three hours after multiple product application. All these values were statistically significant.

#### Example 14

A test of the ability of a retinol containing composition to enhance the rate of cellular turnover in the epidermis was conducted. The human epidermis represents a cell renewal system in which fully differentiated cells (corneocytes) are being continually shed from the skin surface. Since this system operates under steady-state conditions, this loss of desquamated cells must be balanced by

new cell production in the germinative cell layers. One parameter that is especially important to measure in such a system is transit time - the time required for a cell to move through a compartment. Since cells move in unison as a layer through the stratum corneum,, this means, in this special case, that transit time is equivalent to turnover time - the time required for a compartment to completely renew itself.

Previous studies have shown that the turnover time of the stratum corneum can be measured nonintrusively by impregnating it with a fluorescent marker dye that binds avidly to the nonviable corneocytes but not the underlying viable epidermal cells. Thus, the time required for the dye to disappear, which can be monitored by Wood's lamp examination, is an indication of the turnover time of the stratum corneum. Therefore,, any difference in the time required for the dye to disappear from a treated and a nontreated site can be considered to be an expression of that product's ability to enhance epidermal renewal.

A test of fifteen healthy female subjects aged 25-45 participated in the study. One arm site was untreated, the other was treated with a composition according to the present invention comprising:

	Demineralized Water	32.08388
	Gly Acrylic Polymer (Lubragerl)	20.00020
25	Cyclomethicone-Tetramer	14.45852
	Cyclometh/Dimeth Copolyol 90/10	10.00000
	Cyclomethicone-Pentamer	3.50064
	Petrolatum	5.00000
	Ethylhexyl Palmitate	5.00000
30	Alcohol SD 40B Anhydrous	4.00000
	Phenyl Benzimidazole-5-Sulf Acid	2.00000
	Triethanolamine 99%	1.10000



- 23 -

	Stearyl ETO (20M) Alcohol	1.00000
	Sodium Chloride	1.00000
	Hyaluronic Acid Sod. Salt	.03960
	Methylparaben	.40000
5	Butylated Hydroxytoluene	.22000
	Retinoid Blend (Example I)	.02088
	Germall	.17600
	Beta-Carotene	.00028

A two week pretreatment was conducted during which time  
10 the composition was applied to the test site twice daily  
(excluding the weekends). Dansyl chloride stain was then  
administered to both the treated and untreated sites. This was  
followed by a 3-5 week period during which the twice daily  
application of the present composition to the treated site was  
15 continued.

The results of this study indicated that the test  
product enhanced epidermal cell renewal by approximately 25%  
over no treatment.

#### Example 15

20 A test of the retinol containing composition of Example  
14 to induce retinoid benefits to the skin was conducted. The  
composition (Example 14) was applied to the upper inner arm of  
ten women aged 25-45 twice daily for a seven week period.  
Superficial shave biopsies of the epidermis were taken from the  
25 treated site and from an adjacent untreated control area.  
Histological observations for retinoid effects were made by a  
leading clinical dermatologist.

The results of this study indicated that retinoid  
effects were observed in 30% of the panelists. These effects  
30 included improvement in vertical orientation and cellular  
stacking in the epidermis and slight increase in the size of

the cells. Further, 20% of the panelists demonstrated an increase in viable epidermis thickness.

### Example 16

Rhino mouse skin studies were conducted to determine the effectiveness of retinol in normalizing epidermal skin structures. Rhino mice normally have wrinkled, sagging skin. The rhino mouse test is used as a model for showing the effects of compositions on the epidermis. In the test each set of seven mice was treated for five days/week for six consecutive weeks. Five sets of mice were treated. The treating agents were similar to the vehicles of formulation J in Example 9 without the retinol blend and that vehicle with the retinol blend, with the retinol content at concentrations of 0.005, 0.01, and 0.03 weight percent. Specifically, the four silicone emulsions contained:

	I	II	III	IV
Demineralized Water	32.08388	32.08388	32.08388	32.08388
Gly Acrylic Polymer (Lubragel)	20.00020	20.00020	20.00020	20.00020
20 Cyclomethicone-Tetramer	14.44968	14.45852	14.41955	14.46924
Cyclometh/Dimeth Copolyol 90/10	10.00000	10.00000	10.00000	10.00000
Cyclomethicone-Pentamer	3.50064	3.50064	3.50064	3.50064
25 Pentrolatum	5.00000	5.00000	5.00000	5.00000
Ethylhexyl Palmitate	5.00000	5.00000	5.00000	5.00000
Alcohol SD 40B Anhydrous	4.00000	4.00000	4.00000	4.00000
Phenyl Benzimidazole-5-Sulf Acid	2.00000	2.00000	2.00000	2.00000
30 Triethanolamine 99%	1.10000	1.10000	1.10000	1.10000
Stearyl ETO (20M) Alcohol	1.00000	1.00000	1.00000	1.00000
Sodium Chloride	1.00000	1.00000	1.00000	1.00000
Hyaluronic Acid Sod. Salt	.03960	.03960	.03960	.03960
Methylparaben	.40000	.40000	.40000	.40000
Butylated Hydroxytoluene	.22000	.22000	.22000	.22000
35 POE (20M) Sorbitan Monolaurate	.03000	-----	-----	-----
Germall	.17600	.17600	.17600	.17600
Retinoid Blend (Example I)	-----	.02088	.06013	.01044
Beta-Carotene	-----	.00028	-----	-----

Visual observation of the skin condition during the period of treatment showed significant diminution of the characteristic epidermal utriculi and an increase in viable epidermal thickness in the sets of mice treated with the present formulations containing retinol when compared with the sets of mice either untreated or treated with the vehicle alone.

#### Example 17

A test of the effectiveness of the formulation in Example 14 to visibly reduce tiny dry facial lines in the crowsfeet areas was conducted to assess its moisturizing ability. Twenty-eight women who were prescreened for lines in the crowsfeet area participated in the study. Panelists applied the test product twice daily for at least two weeks to only one side of the face and left the other side untreated to serve as the control site. After application of the composition of Example 14, a trained evaluator, who had no knowledge of the treatment side, rated the panelist's lines on both sides of the face. The results of this study indicated that there was a statistically significant visual improvement in the number and depth of fine dry lines after just seven days application of the test product.

#### Example 18

A test of the ability of the composition of Example 14 to reduce skin dryness was conducted. Twelve panelists who demonstrated skin dryness upon repeated soap washing of the hands were selected to participate in this study. Initially, the panelists induced a condition of dryness by washing their

hands with bar soap. The test product was applied daily to one hand while the other was left untreated to serve as a control side. Each hand was rated randomly by two trained evaluators who had no knowledge of which hand had been treated. The  
5 evaluators used a stereomicroscope to assist them with their ratings. The results of this study revealed that effective moisturization benefits were demonstrated throughout treatment by the composition of Example 14. In addition, these benefits persisted for twenty-four hours after the final treatment  
10 indicating that the test product provides effective long-lasting moisturization.

It will thus be appreciated that moisturizing efficacy can be achieved with the compositions of the present invention containing the retinol, thereby precluding the need for a  
15 separate moisturizer. Therefore, preferred compositions of the invention can be formulated to include moisturizing components that are compatible with the alcohol lotion or silicone emulsion to a level of up to 35% by weight of the final formulation.

20 Many modifications of the present invention will be apparent to those skilled in the art. Accordingly, the present invention should be limited only by the spirit and scope of the present claims.

WE CLAIM:

1. A composition comprising retinol, a volatile silicone and a mutual solvent for retinol and the volatile silicone.
- 5           2. The composition of Claim 1 wherein the volatile silicone is cyclomethicone.
3. The composition of Claim 1 wherein the mutual solvent is ethanol.
4. The composition of Claim 1 wherein the weight ratio  
10   of silicone to mutual solvent is 6:4.5.
5. The composition of Claim 1 comprising:  
            retinol;  
            at least 20 weight percent cyclomethicone;  
            25 to 60 weight percent ethanol; and  
15           0 to 15 weight percent emollient.
6. The composition of Claim 5 containing 0.005 to 1.0 weight percent retinol.
7. The composition of Claim 5 containing 0.01 to 0.50 weight percent retinol.
- 20           8. The composition of Claim 1 containing greater than 1.0 weight percent retinol.
9. A composition comprising the composition of Claim 8 and a cosmetically acceptable vehicle in an amount sufficient

to reduce the level of retinol to between 0.005 and 1.0 weight percent.

10. The composition of Claim 9 wherein the vehicle is a water in oil emulsion.

5           11. The composition of Claim 10 wherein the weight ratio of, the oil phase to the water phase is about 1:2.

12. The composition of Claim 9 containing:

0.1 to 1.0 weight percent retinol; and

15 to 35 weight percent cyclomethicone.

10           13. A method of reducing skin wrinkles comprising topically applying to the skin the composition of Claims 6, 7, 9, 10, 11 or 12.

14. The method of Claim 13 further comprising applying a skin moisturizer to the skin at substantially the same time as  
15 the retinol composition is applied.

15. The method of Claim 14 further comprising including a skin moisturizing ingredient in the composition of claims 6, 7, 9, 10, 11 or 12.

16. The composition of Claim 9 further comprising a  
20 moisturizing ingredient selected from the class comprising gly acrylic polymer, petrolatum, ethylhexyl palmitate, and hyaluronic acid sodium salt.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/00780

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>4</sup> A61K 31/07 U.S. 514/725		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	514/725	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup>		
Category *	Citation of Document, <sup>16</sup> with Indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
Y	US, A, 4,224,319 (MERCADET), 23 September 1980, see the entire document	1-16
Y	US, A, 4,423,041 (CLUM), 27 December 1983, see the entire document	1-16
Y	US, A, 4,425,364 (VANLERBERGHE) 10 January 1984, see see the entire document	1-16
Y	L. KLIGMAN, "The Effect on Rhino Mouse Skin Of Agents Which In- fluence Keratinization and Ex- foliation," The Journal of Investigative Dermatology, Vol. 73, No. 5, Part 1, pages 354 to 358, see the entire document. Pub. Williams & Wilkins Co., Baltimore, Maryland, U.S.A.	1-16
<p>* Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family.</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search *	Date of Mailing of this International Search Report *	
2 July 1986	10 JUL 1986	
International Searching Authority *	Signature of Authorized Officer <sup>19</sup>	
ISA/US	LEONARD SCHENKMAN	